Pandemic Influenza Planning and Preparing (for the Unknown)

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Pandemic Influenza Planning and Preparing
(for the Unknown)
2008 NASA Occupational Health Conference

Boris D. Lushniak, MD, MPH

- No relationship with commercial supporters
- No off-label discussion of drugs or devices
- Federal government employee
- Work supported by US Government

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Overview

- Background to influenza
  - Seasonal, avian, pandemic influenza
- Planning and preparation
  - Federal level
- Countermeasures
  - FDA role
  - Vaccines, antivirals, diagnostics, masks, infection control
- Flu Planning
  - Health care, individuals/families

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Influenza

- I had a little bird, its name was Enza, I opened the window and in-flu-Enza.-- American Skipping Rhyme circa 1918

- Latin ‘influentia’ – influence of the stars

Terminology

- Seasonal or common influenza
- Avian influenza
  - H5N1
- Pandemic influenza

Seasonal Influenza

- Annual respiratory illness transmitted from person to person
- Impact
  - Globally 250,000- 500,000 deaths each year
  - As high as 20% morbidity in the US
  - Approx 36,000 deaths and 226,000 hospitalized in US
  - Total annual cost in US over $10-30 billion

Seasonal Influenza

- Caused by orthomyxovirus
  - Negative stranded RNA viruses
  - Type A classified by subtype and strain
  - Type B found only in humans, less severe epidemics
  - Type C may cause mild illness in humans and do not cause epidemics

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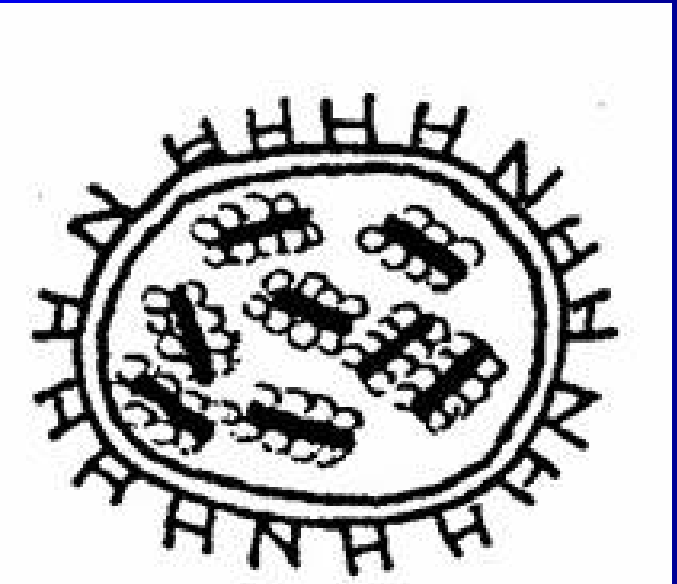
Orthomyxovirus Type A

- Subtypes determined by viral proteins on surface
  - Hemagglutinin (H) – latch onto cells (16 subtypes)
  - Neuraminidase (N) – enzyme that helps virus spread (9 subtypes)
  - Currently circulating in humans H1N1, H1N2, H3N2



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Orthomyxovirus Type A

- Wild birds are natural hosts for all known subtypes of A
  - Low pathogenic avian influenza (H7N7, H9N2, H7N2)
  - Highly pathogenic avian influenza (H5N1, H7N7, H7N3)

- Can infect people, birds, pigs, horses, other animals

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How Influenza Viruses Change

- Dynamic and continuously evolving viruses
- Antigenic **drift** -- small changes to surface proteins through point mutations produces different strains
- Antigenic **shift** – large fragments of genetic material replaced with genes from other influenza subtypes results in new subtype which is perceived by immune system as new

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Influenza Virus Transmission

- Respiratory route
  - Primarily by large droplets
  - Possibly small particle "short distance" aerosols
- Contact
  - Hand contact with secretions

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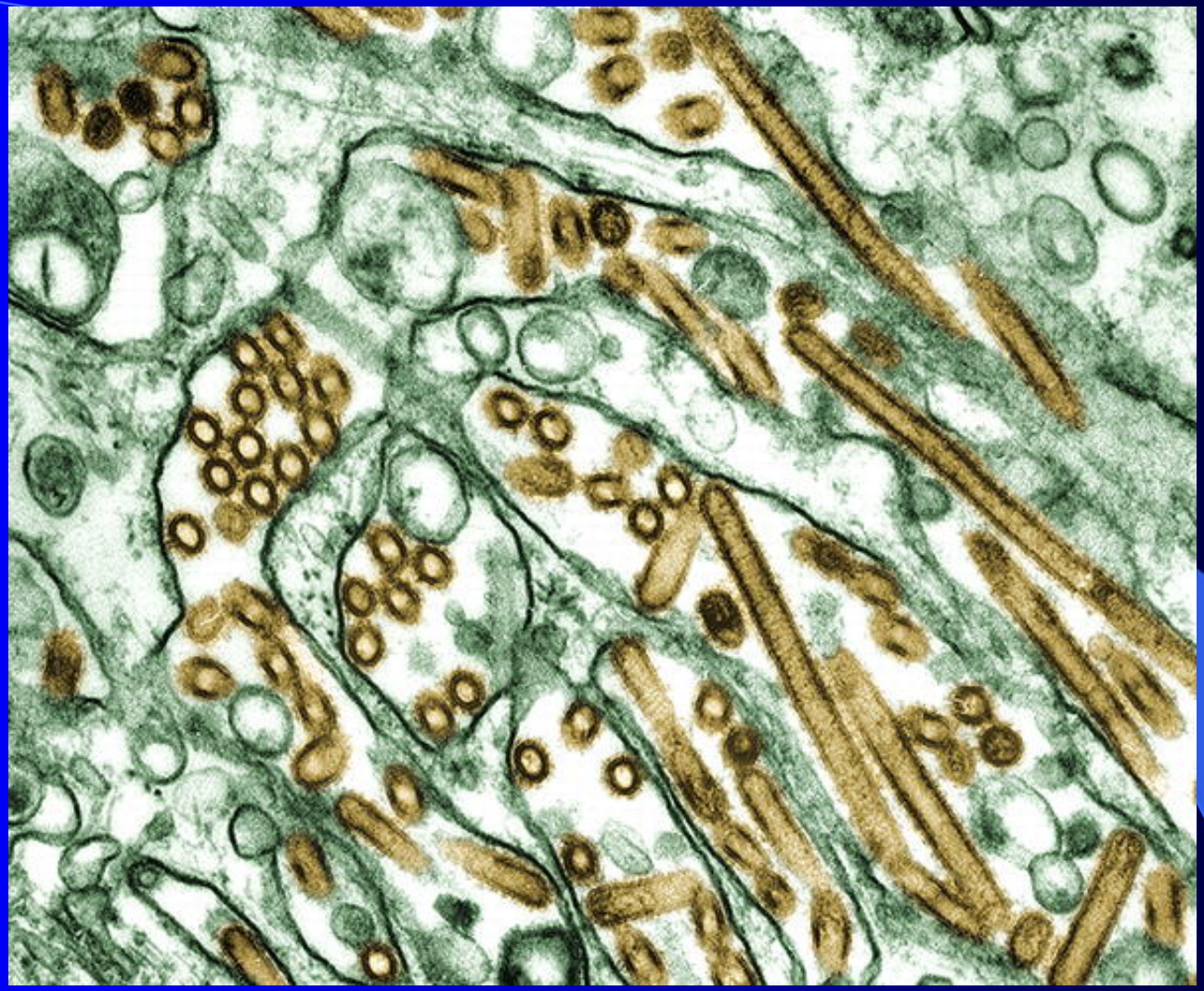
Avian Influenza

Avian or bird flu – caused by influenza viruses that occur naturally among wild birds



Colorized Transmission Electron Micrograph
of Avian Influenza A H5N1 Viruses Grown in MDCK Cells

The viruses are gold, and the MDCK cells are green.

(Photo: CDC/C. Goldsmith, J. Katz, and S. Zaki)

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H5N1 Avian Influenza

- 1996 – H5N1 isolated from a goose in China
- 1997 – Outbreaks in poultry in Hong Kong

- May 21, 1997 – 3 yr old boy dies from H5N1 in Hong Kong
- By Dec 1997 – 18 people infected in Hong Kong and 6 die
  - 1.5 million chickens in Hong Kong culled

- February 2003 – 2 human cases in Hong Kong (father/son)
- 2004 – 47 cases in Thailand and Viet Nam and 34 die

- From 2003 to June 19, 2008 -- 385 confirmed human cases and 243 deaths (63%) in 15 countries

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H5N1 Avian Influenza
Why we are concerned!

- Especially virulent
- Spread by migratory birds
  - In saliva, secretions, feces
  - Now in birds in > 50 nations in Asia, Europe, Africa
- Can be transmitted from birds to mammals (in some cases humans)
  - Concern: May 2006 – Indonesia reports large family cluster (7 cases from 4 households)
- Like other influenza viruses, it continues to evolve
  - Additional strains of H5N1 – clades 1 and 2 which are antigenically different

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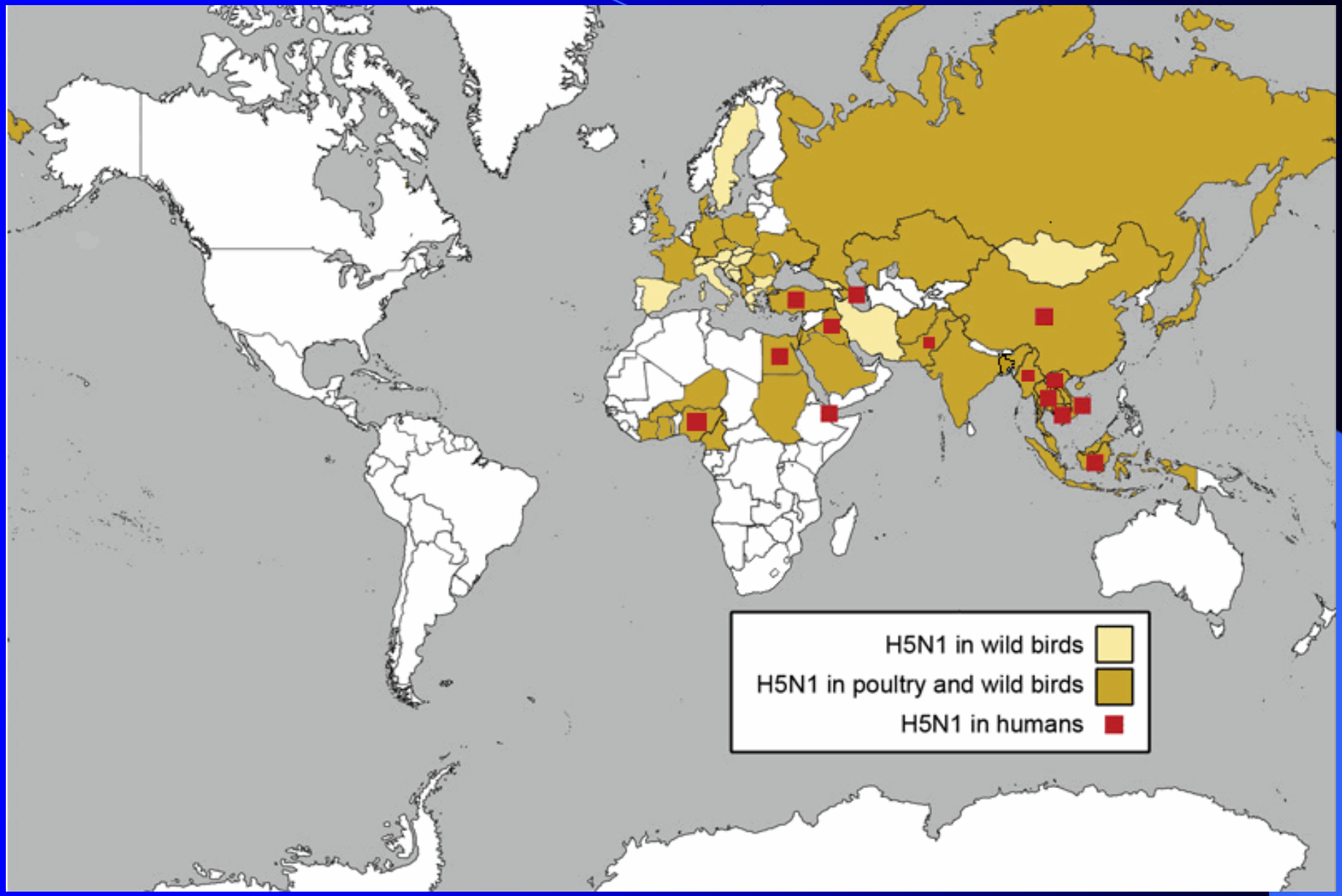
Avian Influenza

- There are other subtypes of concern–
  - H9N2 (mild symptoms; China/ Hong Kong 1999; 2003)
  - H7N2 (Virginia, New York 2002; 2004
  - H7N7 (conjunctivitis; Netherlands 2003)
  - H7N3 (Canada 2004)
  - H10N7 (Egypt 2004)

H5N1 in the World – Birds, Poultry, Humans Feb 2008



WATERFOWL FLYWAYS OF NORTH AMERICA

Pandemic Influenza

Pandemic flu – virulent human flu that causes a global outbreak

- Viral equivalent of “the perfect storm”
- Explosive, global event in which most (if not all) of the world population is at risk
- Believed to have occurred at unpredictable intervals at least over the last 300 years

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Pandemic Influenza

- Three essential conditions
  - A new subtype of influenza virus must emerge from the animal reservoir (no immunity in humans)
  - Virus produces serious illness in humans
  - Virus must be able to spread efficiently from person to person

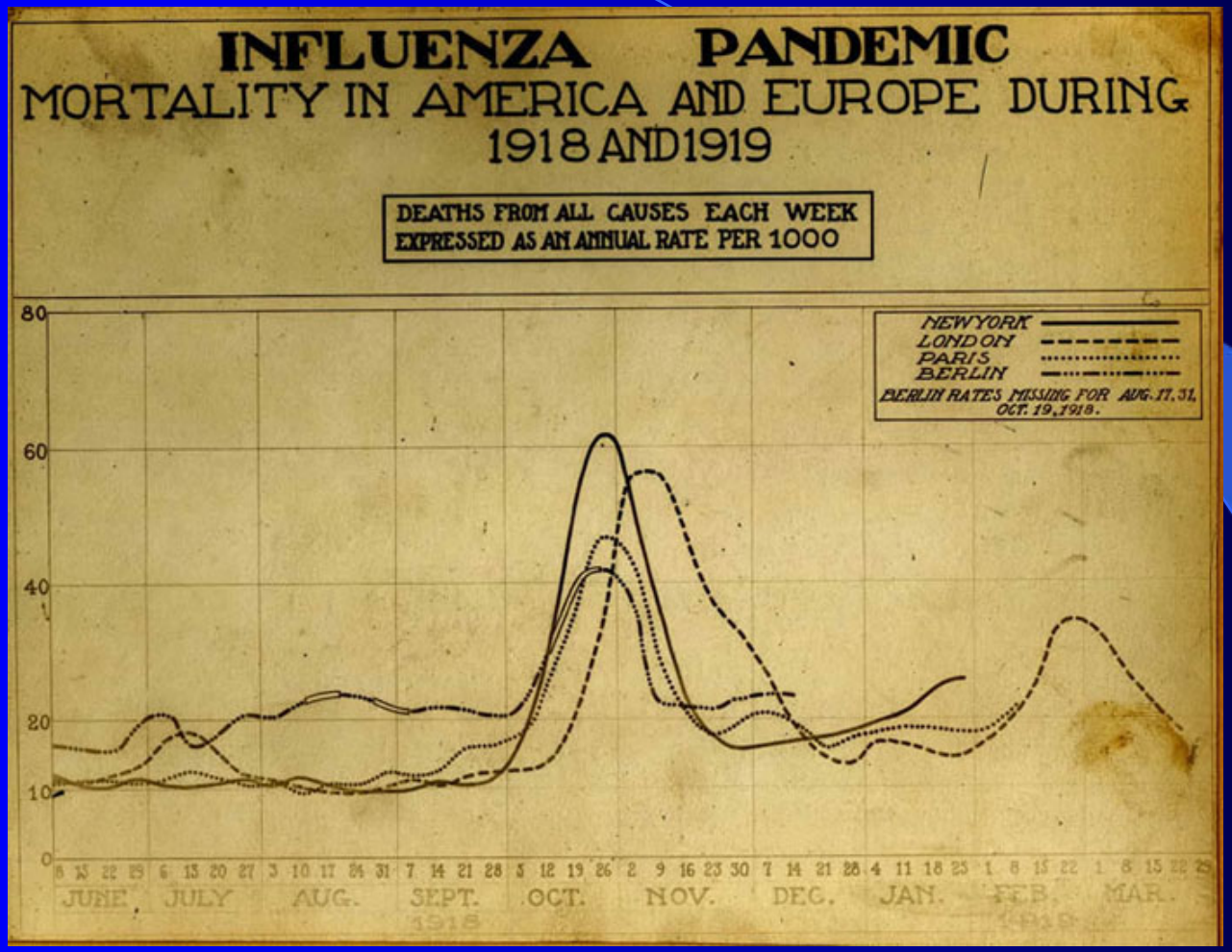
Pandemics

	1918-19	**1957-58**	**1968-69**	?
World Deaths	40-50 million +	1-2 million	700,000	
US Deaths	675,000 (young adults)	70,000+ (infants, elderly)	34,000+ (infants, elderly)	209,000 to 1.9 million ?
Type **Other**	Spanish flu H1N1 Infected 20-40% of world	Asian flu H2N2 To US in 4-5 mos; Global in 8 months	Hong Kong flu H3N2 To US in 2-3 mos	H?N? 865,000 to 9.9 million hospitalized?

Pandemic Influenza 1918-1919

- JAMA Dec 1918 – "The 1918 has gone: a year momentous as the termination of the most cruel war in the annals of the human race; a year which marked, the end at least for a time, of man's destruction of man; unfortunately a year in which developed a most fatal infectious disease causing the death of hundreds of thousands…Medical science for 4 ½ years devoted itself to putting men on the firing line and keeping them there. Now it must turn with its whole might to combating the greatest enemy of all –infectious disease."

Pandemic Influenza 1918-1919



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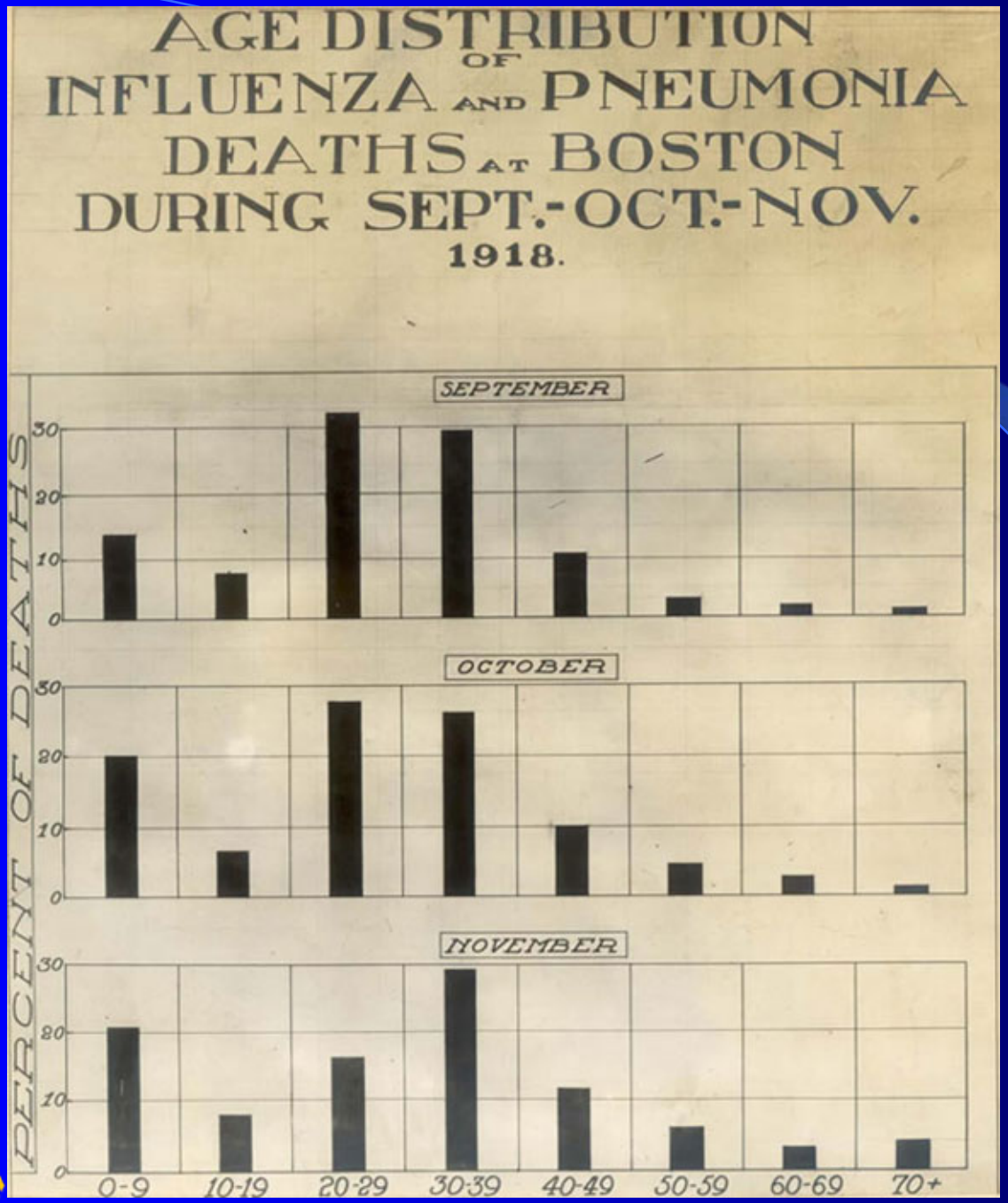

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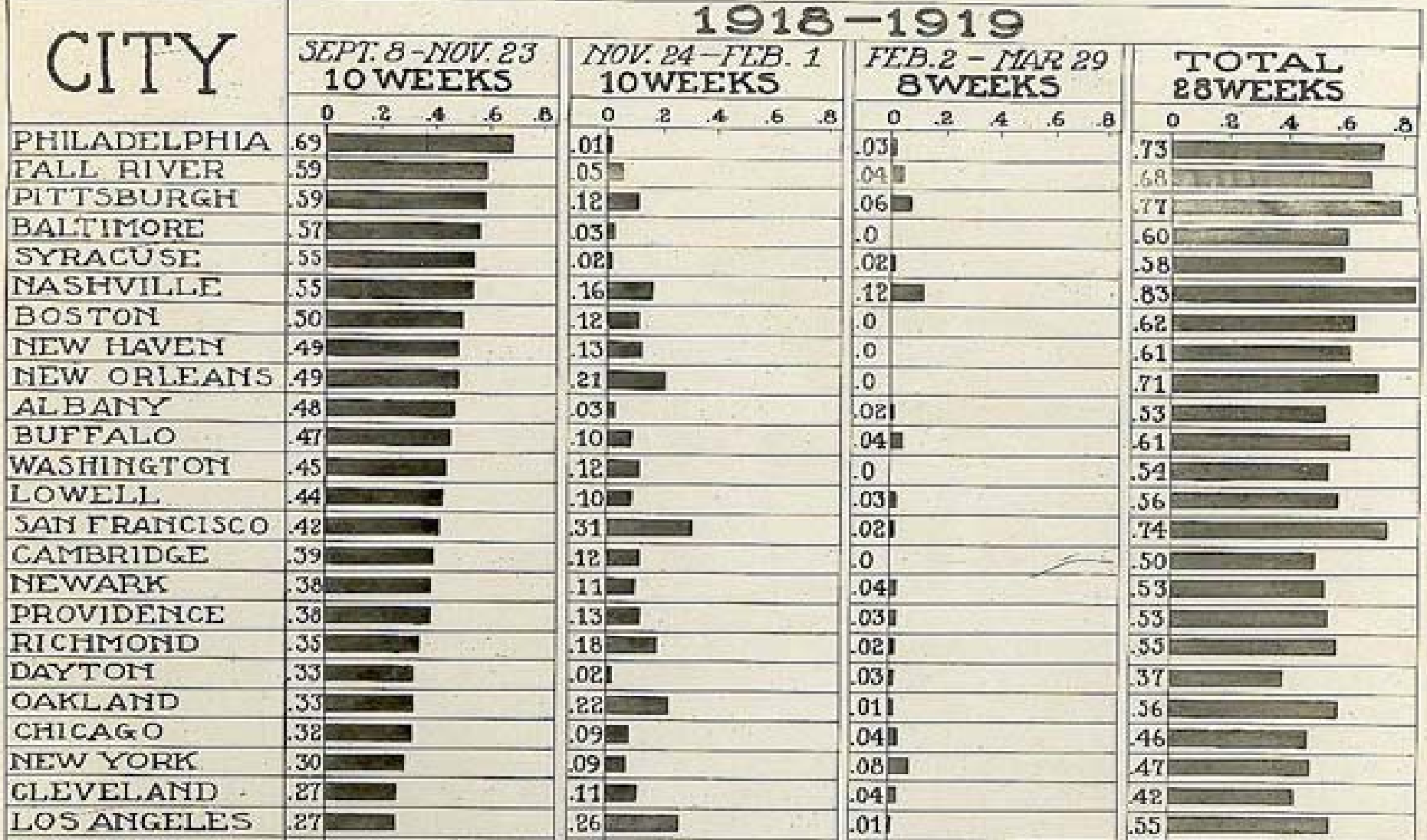
EXCESS MORTALITY IN U·S·CITIES DURING INFLUENZA EPIDEMIC

PERCENT OF POPULATION DYING



Pandemic 1918

- "Our beds were filled as fast as emptied"
  - US PHS Officer Jo Cobb, Chicago Marine Hospital

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Special Daily Press Service, Department of Health Chicago, 10/24/1918

Influenza Dont's

Don't live in the dark Don't shut the sunshine out of your home
Don't exclude the fresh air Don't fail to keep clean
Don't go into crowed places
Don't associate with people who sneeze and cough in your presence
Don't use common towels Don't fail to practice what you preach
Don't overtax your physical powers. Cut out evening entertainments.
Be in bed by ten o'clock.
Don't fail to sleep with every window in your bedroom open.
Don't fail to call your doctor for yourself or any other member of your Family at the first sign of illness. Better be safe than sorry.
Don't allow your home to become damp, chilly, or uncomfortable.
Don't fail, if possible, to walk to your work in the morning and to your home at night. The open air exercise will be of decided benefit.

For newspaper cartoonists, the pandemic was a field-day: street arabs pictured in Joseph Pulitzer's *New York World*

INFLUENZA

FREQUENTLY COMPLICATED WITH

PNEUMONIA

IS PREVALENT AT THIS TIME THROUGHOUT AMERICA.

THIS THEATRE IS CO-OPERATING WITH THE DEPARTMENT OF HEALTH.

YOU MUST DO THE SAME

IF YOU HAVE A COLD AND ARE COUGHING AND SNEEZING DO NOT ENTER THIS THEATRE

GO HOME AND GO TO BED UNTIL YOU ARE WELL

Coughing, Sneezing or Spitting Will Not Be Permitted In The Theatre. In case you must cough or Sneeze, do so in your own hand kerchief, and if the Coughing or Sneezing Persists Leave The Theatre At Once.

This Theatre has agreed to cooperate with the Department Of Health in disseminating the truth about Influenza, and thus serve a great educational purpose.

HELP US TO KEEP CHICAGO THE HEALTHIEST CITY IN THE WORLD

JOHN DILL ROBERTSON

COMMISSIONER OF HEALTH

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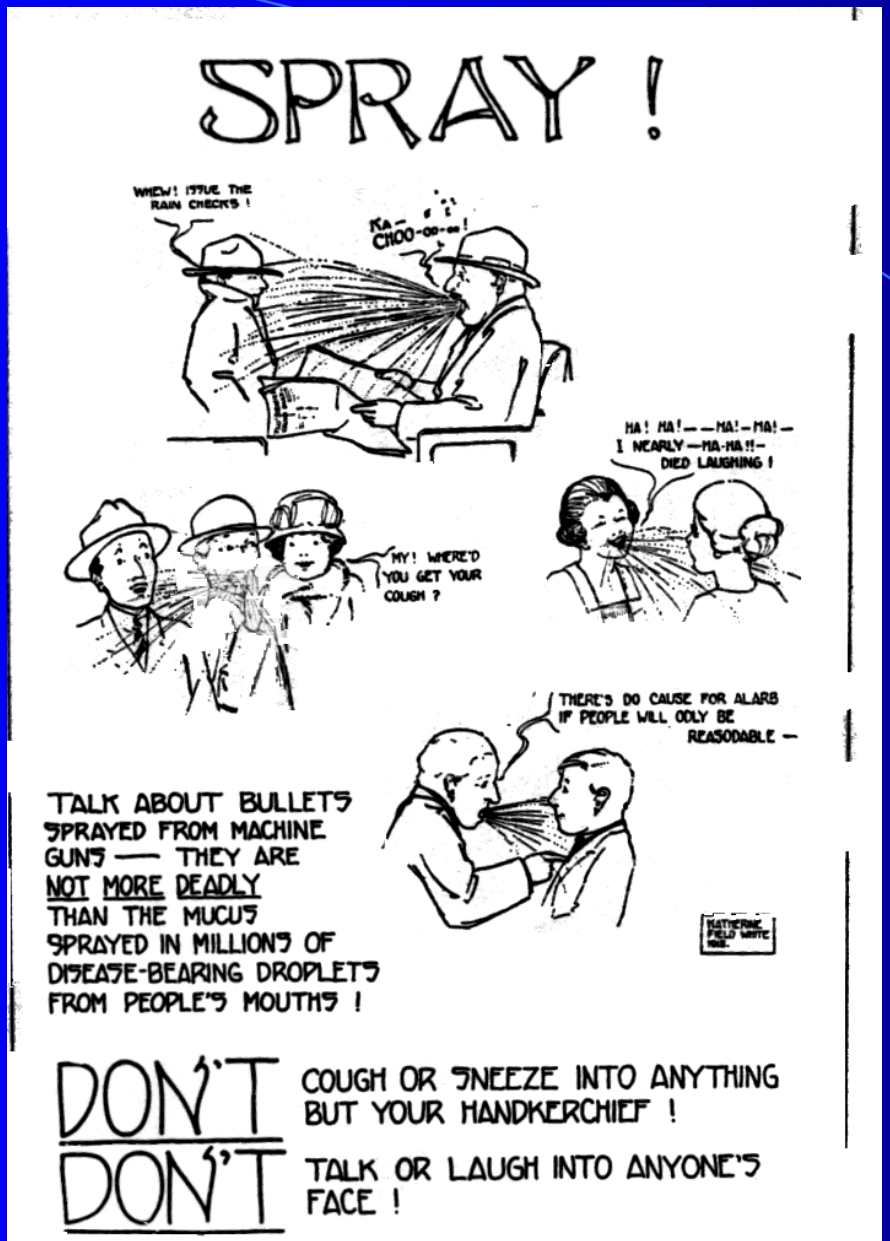

During the statewide influenza epidemic, health agencies used many resources for alerting the public to the contagion. Illinois Health News *carried this pictorial message in the October, 1918. issue.*

Obey the laws
And wear the gauze
Protect your jaws
From septic paws

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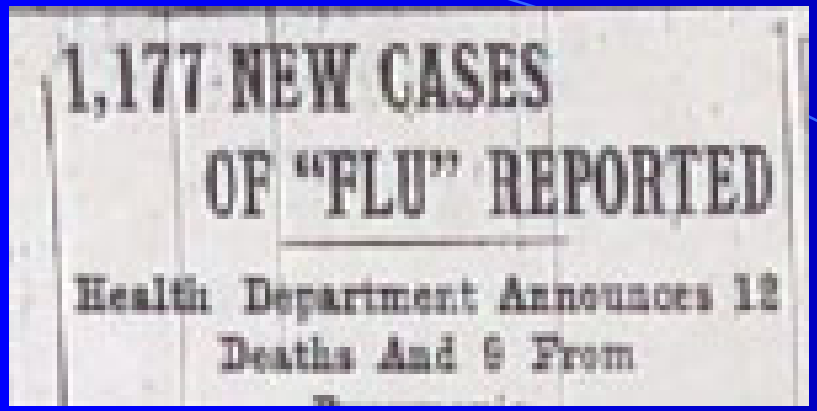
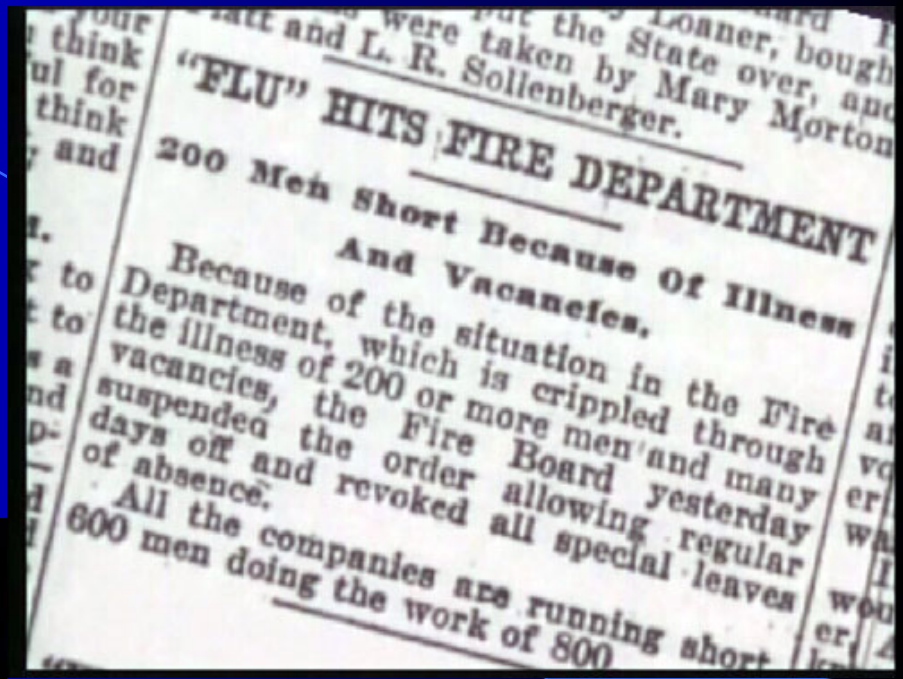


1,177 NEW CASES
OF "FLU" REPORTED

Health Department Announces 12
Deaths And 6 From

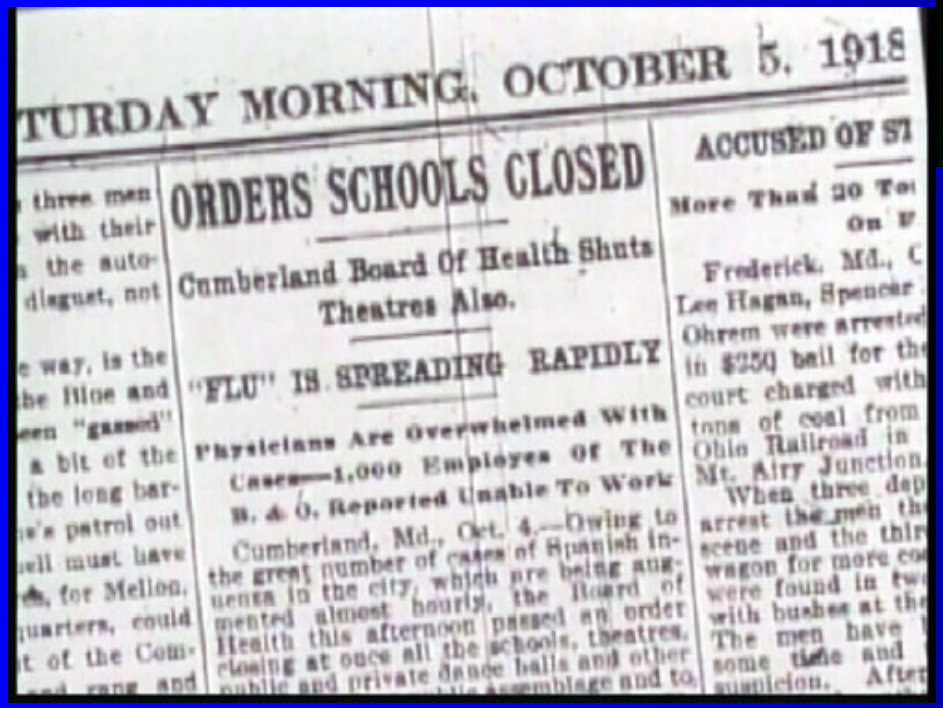


"FLU" HITS FIRE DEPARTMENT

200 Men Short Because Of Illness
And Vacancies.

Because of the situation in the Fire Department, which is crippled through the illness of 200 or more men and many vacancies, the Fire Board yesterday suspended the order allowing regular days off and revoked all special leaves of absence.

All the companies are running short 600 men doing the work of 800



TURDAY MORNING, OCTOBER 5, 1918

ORDERS SCHOOLS CLOSED

Cumberland Board Of Health Shuts Theatres Also.

"FLU" IS SPREADING RAPIDLY

Physicians Are Overwhelmed With Cases—1,000 Employes of The B. & O. Reported Unable To Work

Cumberland, Md., Oct. 4.—Owing to the great number of cases of Spanish influenza in the city, which are being augmented almost hourly, the Board of Health this afternoon passed an order closing at once all the schools, theatres, public and private dance halls and other

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Maryland 1918

- First cases at Camp Meade Sept 17, 1918
- By September 28 there were 1713 cases reported statewide
- By October 12 there were 24, 300 cases reported
- Hospitals overwhelmed, 6 wards of patients at Johns Hopkins, with hospital ultimately closing its doors

Baltimore 1918

- City's health officer believed there was "no special reason to fear an outbreak in our city"
- "Drastic measures" would cause panic therefore no closing of schools or ban on public gatherings
- Ultimately 75,000 resident cases with over 2000 deaths

21st Century Trends Affecting Pandemic Impact

- Global population larger and more urbanized
- Levels of international travel greater
- Increased population of elderly and those with chronic conditions

A 1918 Pandemic Today Would Exact a Horrible Toll

- 50% or more of those who become ill will seek medical care

Severe Pandemic (1918-like)	
Illness	90 million (30%)
Outpatient medical care	45 million (50%)
Hospitalization	9, 900,000
ICU care	1,485,000
Mechanical ventilation	745,500
Deaths	1,903,000

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Pandemic Impact

- May come and go in waves lasting 6-8 weeks
- High levels of illness, death, health care system overload, social disruption, basic service disruption, and economic loss
- Limited vaccine and antiviral supplies

WHO Pandemic Phases

- Interpandemic period
  - Phase 1: no new subtype in humans; present in animals
  - Phase 2: animal virus poses a substantial risk in humans
- Pandemic alert period
  - **Phase 3: human infection but no person-to-person****
  - **Phase 4: small human clusters; limited person-to-person**
  - Phase 5: larger clusters
- Pandemic period
  - Phase 6: increased and sustained transmission in humans
- Post pandemic period – back to phase 1

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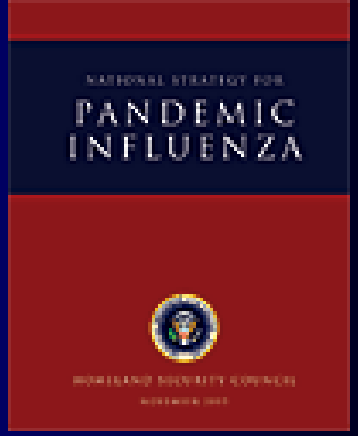
National Planning



- Nov 1, 2005 –Release of the National Strategy for Pandemic Influenza
  - Guides national preparedness and response
  - Stop, slow, or limit spread of pandemic to US
  - Limit domestic spread, disease, suffering, and death
  - Sustain infrastructure and mitigate impact to economy and functioning of society
  - Charges DHHS with leading federal pandemic preparedness

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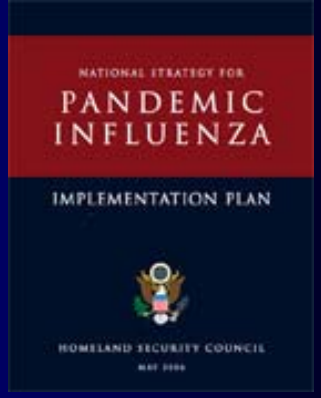
National Planning

- Nov 2, 2005 – the DHHS Pandemic Influenza Plan
  - In coordination with national strategy
  - Guide on how the nation's health system can respond
- Part 1 – Strategic Plan
  - Planning assumptions (30% attack rate; 50% of those seek care; 6-8 week duration with at least 2 waves)
- Part 2 – Public Health Guidance for State/Local Partners
- Part 3 – HHS Agencies' Operational Plans (under development)

National Planning



- May 3, 2006 – release of Implementation Plan for the National Strategy
  - Translates Strategy into over 300 actions for Federal departments and agencies
  - Includes measures of progress and timelines
  - Sets expectations for State and local governments
  - Guidance for States, locals, tribal entities, businesses, schools, communities, NGOs, families and individuals

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Community Strategy for Pandemic Influenza Mitigation
February 2007 Pandemic Severity Index

*Assumes 30% illness rate and unmitigated pandemic without interventions

National Strategy for Pandemic Influenza Implementation Plan
One Year Summary July 2007

SAFEGUARDING OUR HEALTH

- Enhance global and domestic biosurveillance capability
- Coordinate international containment and rapid response
- Prepare to implement layered border measures
- Develop rapid diagnostic tests
- Create ability to care for large numbers of ill
- Stockpile critical medical materiel
- Maintain essential government services
- Sustain critical infrastructure and business continuity
- Communicate accurate and timely information to the public

- Encourage hand hygiene and cough etiquette
- Promote use of facemasks and respirators, as appropriate
- Prepare to implement community mitigation measures
- Expand vaccine production capacity and technology
- Stockpile pre-pandemic vaccine
- Develop ways to stretch our vaccine supply (adjuvants)
- Stockpile antiviral medications
- Educate and inform the public about measures to reduce disease transmission

FDA Mission

Responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation

Roles and Responsibilities of FDA in Pandemic Influenza Preparedness

- Focus on initiatives to proactively facilitate or accelerate development, production and regulatory review of:
  - Vaccines
  - Antivirals
  - Diagnostics and other devices, including personal protective equipment (PPE)

Emergency Use Authorization (EUA)

- Allows for use of "investigational" MCMs during a declared emergency
  - Unapproved products and unapproved uses of approved products
  - Drugs, devices, and biological products
  - Involves a chemical, biological, or radiological/nuclear (CBRN) agent

Pre-pandemic Vaccine

- January 2004 – St Jude Research Hospital obtains clinical isolate of H5N1 and uses reverse genetics to create candidate vaccine
- May 2004 – NIH/NIAID contracts to manufacture pilot lots
- Vaccine trials for candidate vaccines
  - New England Journal March 30, 2006 -- Sanofi Pasteur
  - Lancet May 11, 2006 -- Sanofi Pasteur with and without adjuvant
- April 17, 2007 – FDA approves Sanofi Pasteur vaccine for human against H5N1 (ages 18-64 , 2 IM injections 1 month apart)
  - 45% of those receiving the vaccine showed adequate antibody levels

Pre-pandemic Vaccine

- Current stockpile is approx 13 million doses
  - Goal: stockpile 20 million doses prepandemic
  - Goal: capacity to produce sufficient vaccine within 6 months of pandemic
  - Ultimately will need approximately 300 million doses
- But, a pandemic vaccine cannot be produced until a new pandemic influenza virus emerges and is identified

Pre-pandemic Vaccine

- "We have a vaccine, [but we] fundamentally lack the capacity to manufacture it in sufficient volume in enough time"
  - Sec HHS Leavitt, Nov 2, 2005 Senate hearing

Pre-pandemic Vaccine

- Ultimate surge capacity goal of 300 million doses should be achieved in phases between 2008 and 2013
- However, cannot be achieved through egg-based vaccine production alone (6 month process)
- Antigen sparing (use of adjuvants)
- New delivery methods (intradermal)
- Expand and accelerate investment in cell-based vaccine production technology and recombinant based vaccines
  - May 2006 – over $1 billion in contracts with vaccine manufacturers to accelerate development of new vaccine technologies (cell culture based vs egg based)

Antivirals

- Adamantanes (M2 ion-channel inhibitors).
  - Amantadine and Rimantadine – generics available
- Neuraminidase inhibitors.
  - Oseltamivir – (Tamiflu® by Roche)
  - Zanamivir – (Relenza® by GSK)
- H5N1 is resistant to amantadine and rimantadine; oseltamavir and zanamavir seem to be effective
- DHHS goal of an antiviral stockpile of 81 million courses to cover 25% of US population
  - 50M Federal (SNS), 31M States
  - 6M containment, 75 treatment
  - Currently 40M courses in SNS and 13M in States

Diagnostics

- Feb 3, 2006 – FDA approves new lab test developed by CDC to detect human infections with avian influenza A/H5 viruses (Asian lineage)
- Real-time PCR primer and probe set
- Preliminary results within 4 hours (as opposed to 2-3 days)
- Still needs confirmation to identify specific H5 subtype (e.g., H5N1)
- Distributed to Laboratory Response Network (160 labs in all 50 states)

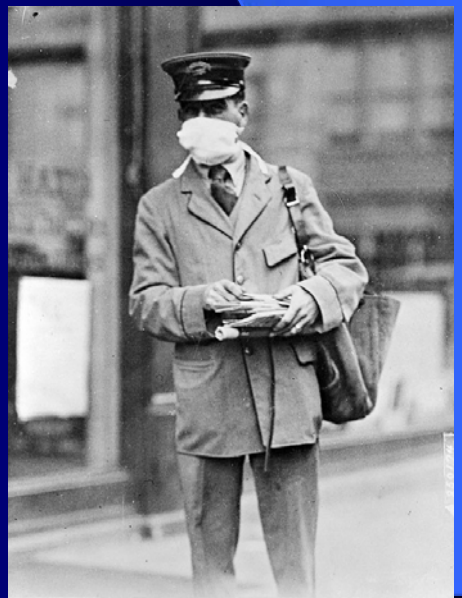
Diagnostics

- January 3, 2008 – FDA clears first test designed to detect and identify 12 respiratory viruses from single sample
- xTAG – can differentiate influenza A subtypes H1 and H3 as well as influenza B
- Multiplex platform amplifies viral genetic material found in secretions from the back of the throat

Diagnostics

- January 18, 2008 – FDA clears real-time PCR for respiratory viruses
- ProFlu+ detects 4 viruses (influenza A and B, RSC A and B) in respiratory secretions from back of throat
- Multiplex platform that allows several tests to be processed uses molecular biology to isolate and amplify viral genetic material

Infection Control



Respirators

- May 8, 2007 – FDA clears first respirators for use in public health emergencies
- Can help reduce the user's exposure to airborne germs during a public health medical emergency, such as pandemic influenza
- 3M N95 filtering facepiece respirator (8612F, 8670F)

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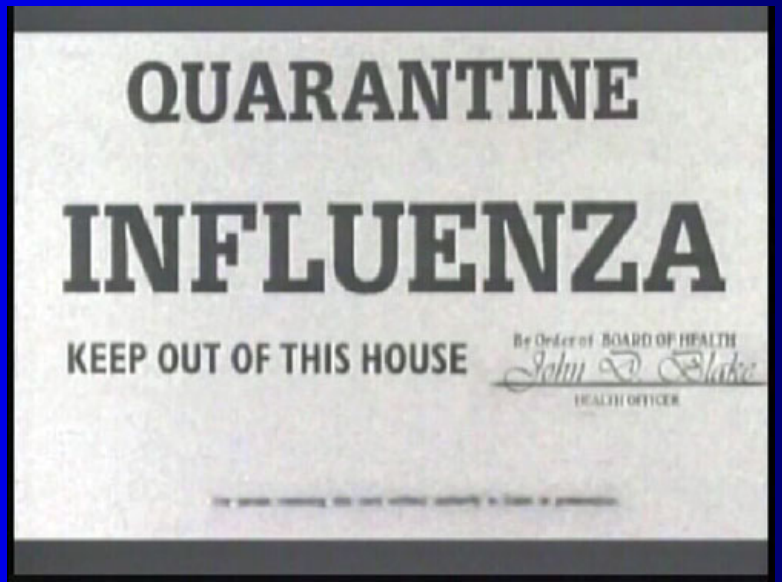
Non Pharmaceutical Interventions

- Isolation and quarantine
- School closures
- Social distancing
- Cancellation of large public gatherings



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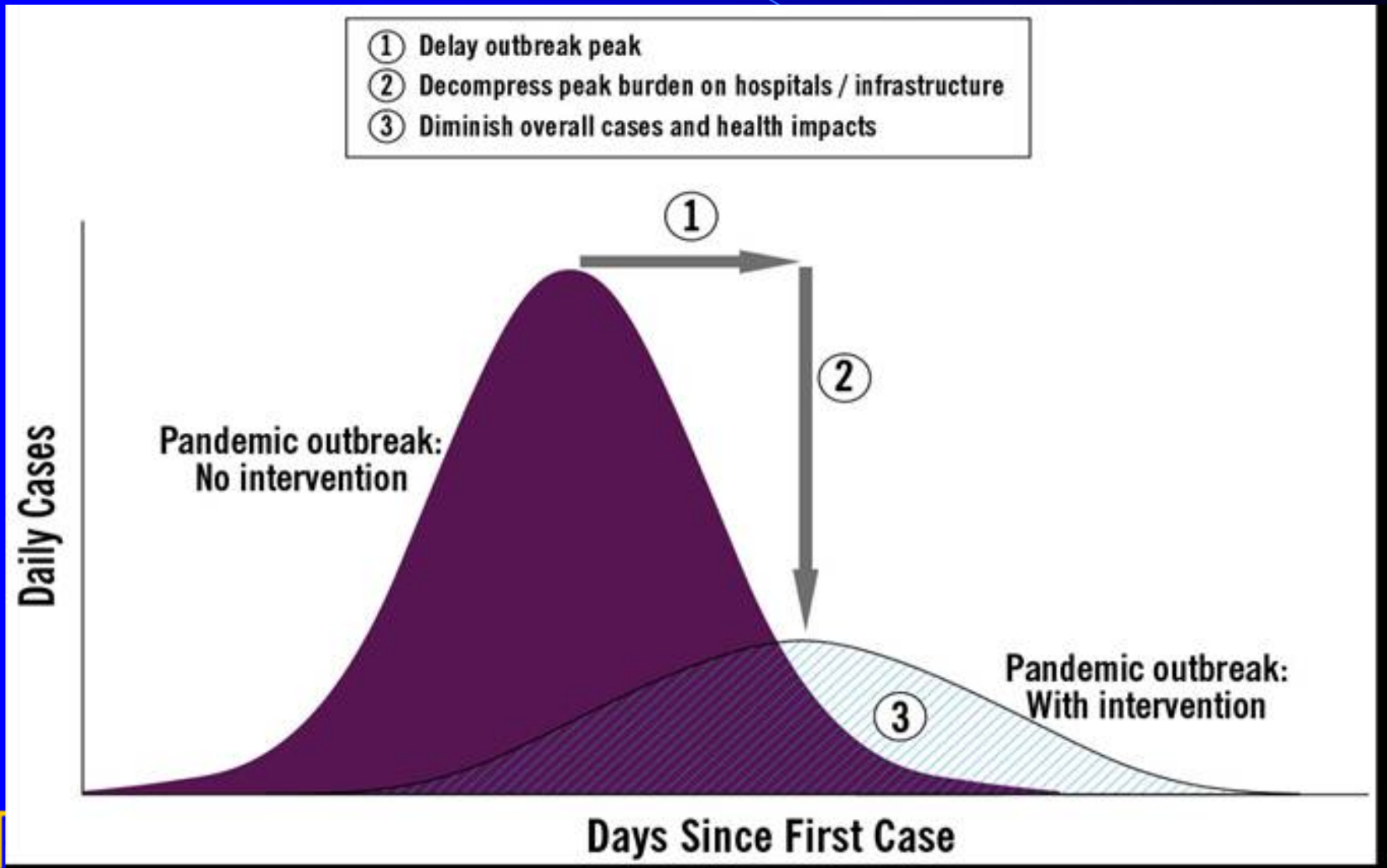
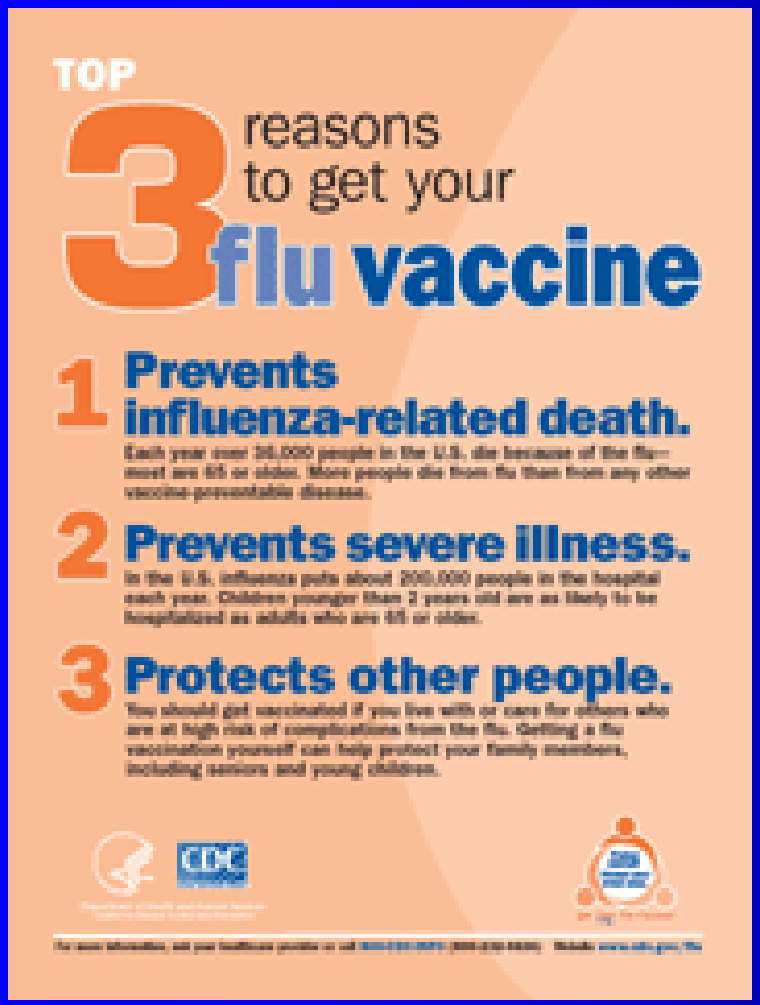
Community Strategy for Pandemic Influenza Mitigation FEB 2007

	Pandemic Severity Index		
Interventions* by Setting	**1**	**2 and 3**	**4 and 5**
Home			
Voluntary isolation of ill at home (adults and children); combine with use of antiviral treatment as available and indicated	Recommend†§	Recommend†§	Recommend †§
Voluntary quarantine of household members in homes with ill persons¶ (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient	Generally not recommended	Consider **	Recommend **
School			
Child social distancing			
-dismissal of students from schools and school based activities, and closure of child care programs	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
-reduce out-of school social contacts and community mixing	Generally not recommended	Consider: ≤4 weeks ††	Recommend: ≤12 weeks§§
Workplace / Community			
Adult social distancing			
-decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)	Generally not recommended	Consider	Recommend
-increase distance between persons (e.g., reduce density in public transit, workplace)	Generally not recommended	Consider	Recommend
-modify, postpone, or cancel selected public gatherings to promote social distance (e.g., stadium events, theater performances)	Generally not recommended	Consider	Recommend
-modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended	Consider	Recommend

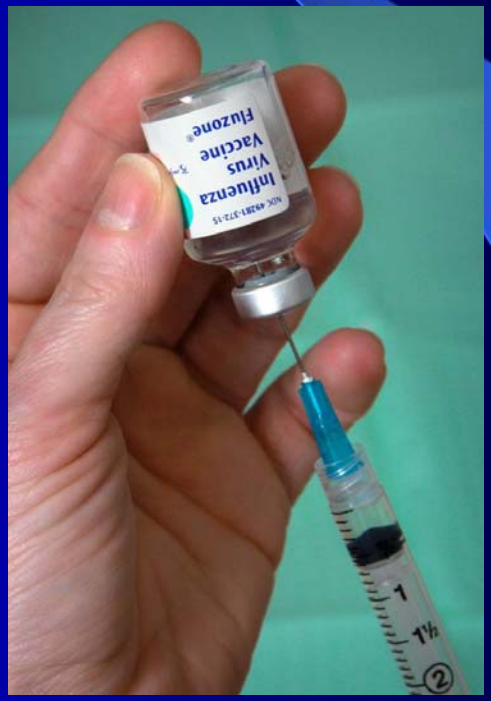
Community Strategy for Pandemic Influenza Mitigation
February 2007 Goals of Community Mitigation



Seasonal Flu Planning



- Age 6 months and older should be vaccinated!!!!!



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Seasonal Flu Vaccine 2007-2008

- Most circulating influenza viruses don't match the vaccine
  - 2 of 3 vaccine components are off target
- When there is a less than ideal match there is still some cross-protection
- WHO meets in Feb to predict what strains will be prevalent in following year
- Also, in 2007-2008, some resistance to Tamiflu

Pandemic Flu Planning
Health Care Planning Checklists

- Home health care services
- Medical offices and clinics
- Emergency medical services and medical transport
- Hospital preparedness
- Long term care and other residential facilities

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What Can You Do? Volunteer

- Medical Reserve Corps
  - www.medicalreservecorps.gov
- National Disaster Medical System (NDMS)
  - Disaster Medical Assistance Teams (DMAT)
  - www.ndms.dhhs.gov

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Pandemic Flu Planning for Individuals and Families

- Store a 2 week supply of water and nonperishable food
- Check you prescription drug supply
- Have health supplies on hand – pain relievers, stomach remedies, cough and cold meds, fluids with electrolytes, vitamins
- Talk with family and loved ones
- Volunteer with your community/local groups to prepare and assist with emergency response

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Pandemic Flu Planning for Individuals and Families

- Teach your children to wash hands with soap and water and do so yourself
- Teach your children to cover coughs and sneezes with tissues and do so yourself
- Teach your children to stay away from others if they are sick and do so yourself. Stay home from work and school if sick.

Pandemic Flu Planning for Individuals and Families

- Plan for the possibility that usual services may be disrupted (healthcare, banks, restaurants, govt offices, telephone companies, post offices, banks/ATMs)
- Stores may close or have limited supplies
- Transportation/travel may be disrupted
- Public gatherings may be cancelled
- Work and schools may be closed

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Pandemic Influenza

"It is clear that pandemic influenza has the potential to pose disease control challenges unmatched by any other natural or intentional infectious disease event." -- DHHS

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DHHS Secretary Mike Leavitt

An influenza pandemic would test our nation's health care system as never before, and this plan anticipates the specific problems we will face and recommends solutions to better protect the American people.

A pandemic will cause disease outbreaks in many different communities all at the same time, making state and local preparedness so important in saving lives.

No one in the world today is fully prepared for a pandemic. But we are better prepared than yesterday, and we'll be better Prepared tomorrow than we are today.

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Review

- The US Public Health Service
- Background to influenza
  - Seasonal, avian, pandemic influenza
- Planning and preparation
  - Federal level
- Countermeasures
  - FDA role
  - Vaccines, antivirals, diagnostics, masks, infection control
- Flu Planning
  - Health care, individuals/families

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www.fda.gov www.PandemicFlu.gov

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